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FURTHER INVESTIGATIONS ON METABOLISM IN FEVER.
ACID-BASE BALANCE DURING FEVER

By Dr. Otto Beck from the University Children's Clinic,
Tübingen (Director: Prof. W. Birk)

Jahrb. für Kinderheilkunde, Vol 113, pp 198-210, July 1926

Introduction

A number of investigations of metabolism in artificially fed infants during vaccine fever, measles, or chickenpox fever, described elsewhere¹), have yielded the results that, in addition to quite definite quantitative changes in nitrogen metabolism, qualitative changes also take place.—Along with changes in the excretion of urea- and amino-acid nitrogen it was primarily ammonia nitrogen that showed a uniform and typical behavior throughout all experiments. A considerable increase of absolute as well as relative ammonia values should be observed in ammonia excretion at the peak of the fever and during the start of convalescence. Not every fever peak was accompanied by a corresponding fluctuation in ammonia nitrogen; this was especially true in the case of small and temporary temperature rises. But as soon as higher temperatures were reached a strong increase in ammonia excretion occurred. Thus these changes in ammonia excretion required for their occurrence a certain severity and a definite period of duration of the fever.

This statement as such is not new. The first investigations on this subject were made by Koppe²) and Hallervoorden³). Both these investigators demonstrated a considerable increase

1) Jahrb. f. Kinderheilkunde (Yearbook of Pediatrics) Vol 112, p 184.

2) Quoted after Hallervoorden.

3) Arch. exp. Path. Pharmak. (Archives of Experimental Pathology and Pharmacology) Vol 12, p 237.

in ammonia nitrogen in adults at the height of an infectious fever. While Koppe offers no explanation for his findings, Hallervoorden considers the increased ammonia excretion a symptom of increased acid excretion in the urine. A similar view is expressed by Krehl¹) when he says that the increased ammonia excretion is an indication of acidosis which in turn constitutes "a phenomenon of infection."

As a rule an increased ammonia coefficient can be considered an expression of an acidotic metabolism. But this is not always pathological. This can be seen particularly in the example of the infant fed naturally, in whom -- despite a distinctly increased ammonia coefficient -- titration showed low acidity and neutral pH values in the urine -- e.g., alkalosis dominated the metabolism. This demonstrates that an increased ammonia coefficient alone does not permit any conclusions with regard to the presence of acidosis.

Koppe and Hallervoorden's investigations have been conducted in adults. Only two investigations have been conducted in infants with a fever, by Gyorgy²). He found a strongly increased ammonia coefficient during high temperatures and during temperature decline, in one infant vaccinated against cowpox and one inoculated against typhus. These findings, however, do not correspond entirely with my own in regard to the timing of increased ammonia excretion.

I have, therefore, examined the acid-base ratio continuously in three infants with vaccine fever, and in two infants during the course of an infection with measles. All the children came from a crèche connected with the children's clinic and were otherwise healthy and free of constitutional defects.

We estimated total nitrogen, ammonia nitrogen, phosphoric acid, excess acid, and titratable acidity of urine, hydrogen ion concentration of urine and tissue fluids, and in one test also the carbon dioxide tension of the blood.

Methods

Total nitrogen was determined according to Kjeldahl, ammonia nitrogen with Folin's ventilation method.

I determined excess acid according to Brock³) (titration

- 1) Krehl-Marchand, Handbuch d. Pathol. (Handbook of Pathology) 1923, p 33.
- 2) Zschr. f. die ges. exp. Med. (Journal of General Experimental Medicine) Vol 43, p 605.
- 3) Zschr. f. klin. Med. (Journal of Clinical Medicine) Vol 100, p. 51.

of 20 cc urine with n/10 lye against a control solution of 0.1 mol sec sodium phosphate. Indicator neutral red.

Titratable acidity was determined in the customary fashion (titration of 10 cc urine with n/10 lye against phenolphthalein, and with n/10 acid against methyl orange).

Phosphoric acid was titrated with uranyl acetate against cochineal dye.

The actual reaction of urine and tissue fluids was found by the colorimetric method according to Michaelis in Walpole's comparator.

The contents of a cantharidal blister applied according to Gänssle's communication was used for tissue fluid.

Blood carbon dioxide content was determined with Barcroft's differential blood gas manometer.

Tests

1st Test. Vaccine fever. Child Zi.

The boy was born on 2 Aug 24 in the Gynecological Clinic and entered the crèche on the 10th day after birth. He was nursed for four weeks, put on mixed feeding for a further four weeks, and then put on half milk, half porridge. Further development was normal. There were neither nutritional disturbances nor infections. The boy was entered in the test on 23 Mar 25. Weight at start of test: 8160 g. Vaccinated with cowpox vaccine on 25 Mar. Distinctly red spots appeared in the vaccinated area on the 6th day, simultaneously the temperature increased. The fever extended over a period of three days and reached its peak at 39.0° on the eighth day after vaccination. Food intake was generally good, only on the day when the fever was at its peak the boy drank about 60 g less milk.

Duration of test 15 days.

2nd Test. Vaccine fever. Child He.

Birth normal and at term in the Gynecological Clinic. Under medical observation in the crèche from the 15th day after birth on. Nursed for three weeks, then on mixed feeding with buttermilk for four weeks, then put on buttermilk with 2% flour and 5% sugar. Normal development, no nutritional disturbances, no infections.

Entered in the metabolism test on 1 Aug at the age of two and a half months. Vaccinated with cow vaccine the same day. Weight at test start 4600 g. Vaccine spots showed reddening on the 7th day after vaccination, simultaneously temperature rose. Peak of fever on the 9th day after vaccination at 39.2°. Fever decreased on the 11th day.

Diet during the test: five times 180 g buttermilk with 2% flour and 5% sugar. Good food intake, increase in weight during 13 test days 110 g.

3rd and 4th test. Measles, then vaccine fever. Child Ma.

The boy was accepted in the crèche at the age of three months. Birth normal and at term in the Gynecological Clinic. Nursed for six weeks, then artificial feeding. Never ill.

At the age of six weeks during a measles infection in the crèche the boy was entered in the test. The probable day of infection could be definitely ascertained, and the boy did indeed come down with measles on the 14th day after the test was started. Despite a very severe rash, increase in temperature was comparatively slight. The highest temperature was 38.9°. Duration of fever during the rash two days. Duration of prodromes with an average temperature of 38°: four days. Weight increase during the test lasting 20 days: 470 g.

On the 13th day some urine was lost accidentally. Therefore this day was not evaluated. Since the boy was exceptionally suitable for metabolism tests, a second test was conducted after an interval of 14 days. In this second test I investigated the effects of vaccine fever.

Vaccination with cowpox vaccine on 14 Aug 25. Distinct reddening of vaccination area on the 6th day after vaccination. Temperature rose to 38.2° on the 9th day. Total duration of fever period: three days. Highest temperature 39°. Diet during this test was the same as during the previous measles test. Average increase in weight 20 g per day. Duration of experiment: 14 days.

5th Test. Vaccine fever, then measles. Child Mo.

The boy was accepted at the crèche at the age of 19 days. Birth normal, at term, in the Gynecological Clinic. Nursed for three weeks, eight days on mixed feeding, then artificial feeding. Never ill. Age at the start of experiment on 31 Oct 25 was five months. The boy was vaccinated with cowpox vaccine on the evening of 30 Oct. Fever began on the sixth day after

vaccination. Highest temperature 38.8° on the 8th day after vaccination. Due to an undesirable coincidence another child who was in the incubation period of measles, was accepted for testing on the same day as this child. He infected with measles -- among others -- also this test child. Febrile prodromes started on the 10th day of the probable infection. On the 13th day Koplik's signs could be demonstrated unambiguously. In addition to this the patient had acute rhinitis and conjunctivitis. On the 14th day a typical measles rash could be seen.

It was intended to continue the test until the period of convalescence but it had to be interrupted on the 15th day because the boy began to become a feeding problem. Duration: 15 days. Increase in weight during test: 300 g. (Compare Fig. 1.)

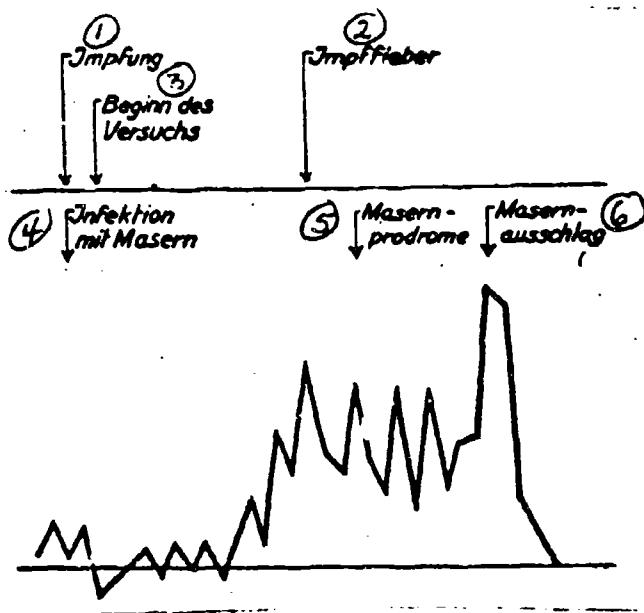


Fig. 1.

1 -- Vaccination; 2 -- Vaccination fever; 3 -- Start of test;
4 -- Infection with measles; 5 -- Measles prodrome; 6 -- Measles rash.

RESULTS

First of all with regard to ammonia nitrogen, it can be seen from the tables as well as from Fig. 2 that in these five tests, too, there undoubtedly is a connection between fever and ammonia excretion.

Test I. Vaccine Fever

(1) Tag	(2) Temp.	(3) N-Harn	(4) Ammonia-N mg.	(5) Prox.	(6) Succo. O.	(7) A + NH ₃	(8) P ₂ O ₅ mg/g	(9) P _b Harn	(10) Gew.
1		3478	173.1	5.4	182	805	167	7.1	
2		3218	249.4	7.7	158	407	153	6.9	
3		3329	113.5	8.2	101	277	140	7.2	
4		3654	119.4	4.6	104	279	141	7.1	
5		3113	235	7.8	167	602	183	6.8	
6		3100	190	6.1	141	331	177	7.2	
7		3920	176	6	150	326	165	7.3	
8		3047	190	4.9	151	255	177	7.3	
9	37.4	3934	318	10.8	165	653	203	6.8	
10	36	3178	387	9.6	100	413	190	6.8	
11	36.8	3619	340	10.7	125	475	193	6.8	
12	37.3	3140	293	11.8	167	451	198	6.8	
13		3134	231	10.7	92	421	186	7.2	
14		3176	278	9.8	113	376	171	7.0	
15		3261	230	7.4	151	271	183	6.8	

-- Day; 2 -- Temperature; 3 -- N, urine; 4 -- Ammonia-N mg;
 5 -- %; 6 -- Excess Acid; 7 -- A + NH₃; 8 -- P₂O₅ mg in %; 9 -- pH urine.

Test II. Vaccine Fever

(1) Tag	(2) Temp.	(3) N-Harn	(4) Ammonia-N mg	(5) Prox.	(6) Succo. O.	(7) A + NH ₃	(8) P ₂ O ₅ mg/g	(9) P _b Harn	(10) Gew.
1		37.9	168	5.1	88	234	93	7.8	7.4
2		3606	189	5.2	119	308	90	7.8	7.4
3		3707	216	5.9	118	334	92	7.8	7.4
4		3529	202	5.6	106	311	97	7.0	7.4
5		3479	228	6.8	123	360	28	7.2	7.4
6		3187	208	6.4	123	334	91	7.1	7.4
7		3198	221	6.5	116	337	99	7.1	7.4
8	36.1	3664	194	5.4	118	304	87	7.1	7.4
9	36.4	3748	163	4.5	118	261	100	7.1	7.4
10	36.3	3575	232	7.1	120	358	181	6.8	6.8
11	36.2	3117	224	7.3	99	258	121	6.8	6.8
12	36	2940	261	8.9	73	234	95	6.8	6.8
13		3265	224	7.7	74	267	82	6.9	7.3

1 -- Day; 2 -- Temperature; 3 -- N, urine; 4 -- Ammonia-N mg;
 5 -- %; 6 -- Excess Acid; 7 -- A + NH₃; 8 -- P₂O₅ mg in %; 9 -- pH urine; 10 -- tissue

Test III. Measles

1		2722	144	5.1	181	275	108	7.8	7.4
2		2942	175	3.8	184	306	121	7.1	7.4
3		2228	168	6.4	185	318	111	7.1	7.4
4		2920	151	4.2	122	291	118	7.1	7.4
5		3013	184.4	4.7	118	256	116	7.2	7.4
6		2940	147	5.0	187	283	112	7.1	7.4
7		3032	155	7.2	126	261	104	7.2	7.4
8		2600	148	5.6	181	268	118	7.2	7.4
9		2600	148	5.6	180	264	121	7.0	7.4
10		2446	145	5.3	181	274	150	7.0	7.4
11		2311	119	5.1	120	236	120	7.1	7.4
12		3162	194	6.1	194	308	178	6.8	7.1

1 Day Interval

14	38	241	225	7.9	190	415	137	6.1	6.8
15	34.9	2672	184	7.1	178	368	153	6.1	6.7
16	38	2647	276	10.2	160	441	168	6.4	6.9
17		2675	971	9.4	155	491	129	6.4	7.0
18		2667	163	6.1	148	226	107	7.3	7.4
19		2415	163	6.5	103	266	111	7.3	7.4
20		2369	158	7.8	126	361	130	7.3	7.4

Test IV. Vaccine Fever

1		3181	130	4.9	188	343	111	6.8	7.4
2		2672	194	4.8	164	394	96	6.9	7.3
3		2663	112	6.1	143	390	96	7.3	7.4
4		2615	136	4.5	170	275	108	7.1	7.3
5		3019	170	5.0	172	343	110	6.8	7.2
6		2600	146.8	5.8	137	301	95	6.8	7.2
7		3038	174	5.0	181	369	114	6.9	7.3
8		2980	177.4	6.1	143	391	101	7.3	7.4
9	34.8	3183	334.3	9.8	158	419	121	7.0	7.3
10		3100	301	9.1	214	418	128	6.1	6.9
11		2624	269	10.2	157	444	131	7.1	7.4
12		2471	244	8.1	145	392	99	7.1	7.2
13		2274	191	8.1	149	361	106	7.3	7.4
14		3038	180	8.9	99	361	98	7.3	7.4

Text V. Vaccine Fever, then Measles

① Tag	② Temp.	③ N-Harn	④ Ammonia-N mg	⑤ P ₂ O ₅	⑥ Excess Acid	⑦ C	⑧ A + NH ₃	⑨ P ₂ O ₅ mg in %	⑩ pH Harn	⑪ G.w.
1		2995	176	6.7	128	361	105	7.3	7.4	
2		3137	244	7.7	157	401	98	7.5	7.4	
3		2841	231	8.1	124	321	104	7.3	7.4	
4		2704	246	9.1	109	361	103	7.3	7.4	
5		2456	218	8.3	177	415	138	6.8	7.4	
6	37.8	2164	244	10	149	369	181	6.6	6.9	
7		2229	216	9.2	129	325	173	6.4	6.8	
8		2276	239	10.3	153	394	180	6.8	6.7	
9		2224	290	13.6	112	402	140	6.4	7.0	
10	37.9	2310	213	9.3	108	351	150	7.1	7.2	
11		2493	223	8.6	118	341	114	7.2	7.4	
12		2670	244	8.4	104	346	107	7.0	7.3	
13		3269	361	11	144	508	190	6.8	7.3	
14	34.8	2898	370	18.1	125	493	120	6.2	7.1	
15	32.1	2306	294	13.8	108	402	108	6.9	7.2	

1 -- Day; 2 -- Temperature; 3 -- N, urine; 4 -- Ammonia-N mg;
 5 -- %; 6 -- Excess Acid; 7 -- A + NH₃; 8 -- P₂O₅ mg in %; 9 -- pH urine; 10 -- tissue

In the first test the onset of fever is accompanied by a powerful increase in (absolute and) relative ammonia nitrogen values.

In the 2nd test the start of increased ammonia excretion occurs only on the day of the highest peak in temperature, e.g., on the third day of fever, while no influence on the ammonia coefficient can be seen during the first two days of fever.

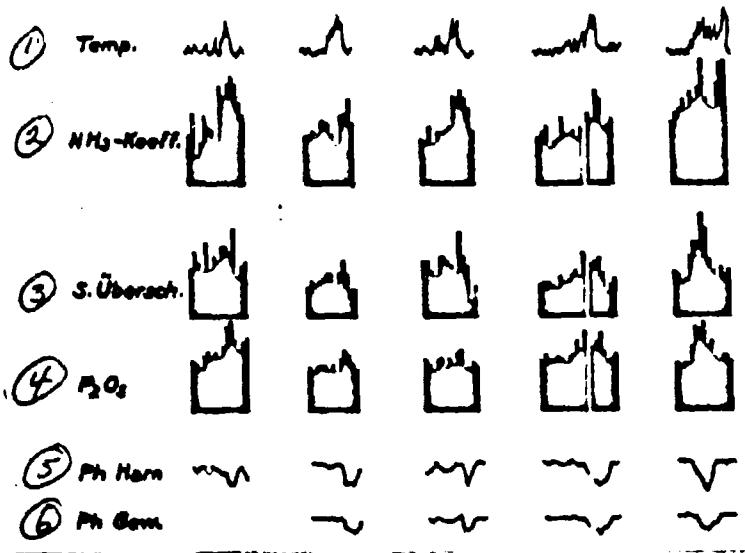


Fig. 2.

1 -- Temperature; 2 -- NH₃ coefficient; 3 -- Excess acid; 4 -- P₂O₅; 5 -- pH urine; 6 -- pH tissue.

Test III shows the same as test I; here, too, the increase in the ammonia coefficient starts on the first day of the fever.

The same holds true for tests IV and V.

The peak of the ammonia curve coincides with the last day of fever in all but the third experiment -- where the greatest amount of ammonia is already excreted on the third day of the fever.

Thus it can be seen that in all experiments there exists a close connection between the level of temperature and the amount of ammonia excreted. This is generally expressed by a considerable increase in ammonia values with the onset of the fever. It is obvious, however, that a certain level and duration of the fever are required to reach the highest values of ammonia excretion. It is further important to note that the high ammonia values do not return to the norm at once with a decline in fever but continue well into the period of convalescence and only then return to normal values.

What then is the course of the acid excretion in the urine during the infection?

Excess Acid

I have purposely put the determination of excess acid in the foreground of my investigative methods because there is no doubt that these give a more unambiguous picture on the amounts of acid excreted in the urine than titration of primary and secondary phosphates with lye and phenolphthalein, and with acid and methyl orange, which has hitherto been customary. With this method neither phosphates alone nor the total amount of weak acids of the urine can be determined. "Excess acid" means that amount of lye which has to be added to a certain quantity of urine to equate its actual reaction to that of blood, e.g., to depress it to a pH of 7.4. We learn nothing, however, about the type of acid appearing in the urine -- whether organic or inorganic -- by determining the excess acid. For my problem, however, this plays only a secondary role at present; I was primarily interested in determining whether any acids appear in increased amount in the urine during the course of infection.

The following results were obtained: the tables show the amount of excess acid expressed in cc n/10 lye, calculated on the total amount of urine. We can observe a distinct influence exerted on the excretion of "excess acid" in all experiments during the fever period, which expresses itself in such a manner that -- during the peak of fever -- there is a strong increase in excess acid values.

This is brought out most distinctly in tests I and V, and is also clearly recognizable in tests II, III and IV. The values for excess acid thus show a parallelism with those for the ammonia coefficient. It is striking, however, that in some of the experiments the increase in excess acid is not continued throughout the entire period of increased ammonia excretion -- the excess acid curve returns to normal while the ammonia coefficient is still high. This is the case in test I, also in test II as well as in tests III and IV. In test V the curves for ammonia and excess acid excretion are exactly parallel.

This demonstrates clearly that there is an increased excretion of acid in the urine at the height of the fever. The increased ammonia excretion can thus be regarded as a process of neutralization.

What, however, is the explanation for the fact that the ammonia coefficient is still high while excess acid values have returned to normal -- as is the case after the decline of the fever in tests I through IV?

When evaluating these facts we must keep in mind that the determination of excess acid alone -- as well as determination of the ammonia coefficient alone -- does not give a clear unambiguous picture of the amount of intermediary acids formed. The fact is that part of the acids is at once neutralized by ammonia, thus removed from urea formation and excreted as free ammonia in the urine.

The amount of acid whose neutralization cannot be accomplished by the available ammonia then appears as excess acid in the urine.

The total amount of intermediary acid formed can best be expressed in the formula $A + NH_3$, where A is the amount of excess acid, NH_3 (= absolute ammonia value) represents the amount of intermediary acids neutralized.

When viewed from this point the apparent contradiction in the behavior of the curves for ammonia nitrogen and excess acid can be comprehended. The figures for the quantity $A + NH_3$ are given in the 7th column of the tables. They show that the total acid excretion after the decline of the fever, i.e., at the beginning of convalescence, when the ammonia coefficient is still high, is still higher than the norm, though the values of excess acid, as mentioned before, have already returned to normal. This is the case in tests I and II, but obvious also in tests III and IV.

Test V is the exception. In this test the curves of ammonia and acid values are exactly parallel and return to the norm at the decline of the vaccine fever.

I must point out in connection with this test that the test child was infected with measles by accident on the day of vaccination, e.g., on the first day of the vaccination test, which alters the conditions in this case. The day of the decline of the vaccination fever -- the 19th test day -- was for this child also the first day of febrile measles prodromes. This can be seen clearly from the course of the fever curve.

Looking at the tables one can observe that the ammonia and acid values are not increased during prodromes. But as soon as the actual measles fever sets in, the values of the ammonia coefficient and excess acid shoot up, as do also the values for the total acid excretion. In other words the same process which was observed during the vaccination fever repeats itself. Unfortunately this test could not be prolonged beyond the period of the onset of rash because the boy stopped feeding.

Nevertheless the increase of acid excretion at the height of the measles fever can be seen also in this case.

Actual Reaction

Furthermore I have investigated the actual reaction of the urine in all tests, and in four of the tests also the actual reaction of the tissue fluid. As far as the pH values of urine are concerned the findings correspond with the theoretical considerations, e.g., the actual reaction in all tests is slightly acid or neutral prior to the onset of fever.

With the onset of infectious fever the pH values change to the strongly acid region and remain acid until the decline of the fever. They thus parallel the total acid excretion. This is a further proof for the shift of metabolism in an acidotic direction during the actual period of fever.

The actual reaction of tissue fluids corresponds entirely with the fluctuations in the pH values of urine. Normal values for the actual reaction of tissue fluids have not been described to date. From the pre-test periods of my investigations it can be said that the hydrogen-ion concentration of tissue fluid fluctuates between pH 7.35 and 7.45 which means that it corresponds approximately with the actual reaction of blood. This is the case up to the onset of the fever in all tests. As soon as the actual fever of the infection reaches higher temperatures the pH values of tissue fluids also show a shift to the acid region. The lowering is not quite so much as that of the pH values of urine, but it can nevertheless be clearly recognized in all tests.

As soon as the values of total acidity return to normal, and the actual reaction of urine becomes again weakly acid or neutral, the pH values of the tissue fluid also shift again into the weakly alkaline region.

We can see, therefore, that a complete parallelism exists between the actual reaction of the urine and the tissue fluids.

Phosphoric Acid and Titratable Acidity

In addition to the calculations described above the estimation of phosphoric acid also permits some insight into the relations of the intermediary acid-base metabolism. It is known that in conditions which lead to acidosis there is primarily an increased formation of organic acids. These intermediary products formed as a result of a sluggish metabolism are comparatively very strong organic acids. An accumulation of such

strong acids must be marked by an accompanying displacement from their alkali compounds of the phosphates which represent considerably weaker acids. These are then excreted in the urine in increased quantities. "An excess of acid valences is eliminated in the urine only when phosphoric acid is excreted" (Straub¹).

Taking these considerations into account I have also estimated phosphoric acid in all tests. It can be seen from the tables that the values for phosphoric acid do indeed show a complete agreement with the fluctuations of the ammonia coefficients and excess acid.

Finally, I have also determined the acidity which can be titrated in all tests. The values obtained here are also in full agreement with the values of excess acid; graphically represented, both curves run a similar course. To save space I have, therefore, not incorporated the figures in the tables.

Lastly, the behavior of the carbon dioxide tension of the blood is also in full agreement with the results just elaborated. In one test (III) I have investigated the carbon dioxide content of the venous blood continuously. This yielded the result that the carbon dioxide content of blood remained percentually absolutely constant throughout the period prior to the fever and again during convalescence, while it showed a distinct 10-15% decrease by volume during the actual period of fever, corresponding to the increase in acid excretion.

Thus, proof that metabolism shifts towards acidosis at the height of an infectious fever and during the early part of convalescence seems finally to have been supplied by these investigations.

When we attempt to elucidate the processes which lead to a shift of the metabolism into the acid region, i.e., which lead to acidosis, one might at first think that a certain connection exists between the magnitude of nitrogen excretion and the amount of excreted acids -- considering the findings of Brock² and Hottinger³). Both investigators believe to have found that, on the whole the excretion of organic acids follows that of nitrogen. According to this it would be plausible that

- 1) Verhandlungen des Deutschen Kongr. f. Innere Med. (Proceedings of the German Congress of Internal Medicine), Kissingen, 1924, p 18.
- 2) Zschr. f. klin. Med., Vol 100, p 51 -- Zschr. f. Kinderheilk. Vol 39, p 44.
- 3) Monatsschr. f. Kinderheilkunde (Monthly Review of Pediatrics) Vol 30, p 497.

during a fever -- during which period, according to Birk¹) as well as our own investigations, there is a powerful excretion of nitrogen even in the infant -- the excretion of acids would be similarly increased, thus leading to acidosis.

There is something to be said in favor of such an explanation. But in my opinion it does not suffice to interpret the changes we have described. As can be seen from the investigations just mentioned (Birk¹; author²)) increased nitrogen excretion is seen not only during the actual period of fever but also prior to it and during convalescence, i.e., after it. It would thus follow that we should expect corresponding increased acid excretion during the pre- and post-fever periods. This, however, is not the case in any of the tests. The metabolism was never shifted in an acidotic direction. A different explanation for the occurrence of acidosis during fever seems more plausible to us. As is known, temperature regulation and internal secretion are closely connected. It is known that on the one hand the activity of endocrine glands is influenced by the vegetative nervous system, and on the other hand this system reacts to internal secretion (Tonieszen³)). The thyroid gland, the hypophysis and the adrenal glands are primarily significant for the regulation of temperature.

Experimental investigations on these internal secretions have shown that they have the ability to influence metabolism decisively (Vollmer⁴) and others). In particular the hormones of the hypophysis and the adrenal gland given subcutaneously first bring about acidosis and soon after that lead to alkalo-sis. In view of the close connections which exist between the temperature regulation center and the endocrine glands, we will have to consider first of all the possibility that under the influence of a fever the endocrine glands are under an influence which deviates from the normal. In the final analysis their hormones may lead to a change in cell oxidation and thus to an acidotic orientation of metabolism.

1) loc cit.

2) loc cit.

3) Klin. Wschr. (Clinical Weekly), 1923, p 477 and 525.

4) Klin. Wschr., 1923, pp 117, 529 and 593.